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REVIEW ARTICLE

Dual Roles for Immunity in Gastrointestinal Cancers

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ABSTRACT

Histopathologic examination reveals that most human tumors are associated with diverse immune cell infiltrates, but the roles of host reactions in disease pathogenesis and prognosis remain to be fully clarified. Recent investigations in genetically engineered murine tumor models have uncovered dual functions for immune responses during cancer development and progression. Alterations in tumor cell gene expression profiles and coding sequences may trigger the activation of cytotoxic lymphocytes, which act to restrain tumor growth. In contrast, persistent inflammatory reactions, which may be driven by infection, environmental toxins, or impaired immune regulation, create a microenvironment that fosters tumor cell growth, survival, invasion, and dissemination. The dynamic interplay of these competing responses appears to be a critical event in cancer pathogenesis, with tumor promotion and immune evasion proving dominant in clinically evident disease. Nonetheless, longitudinal studies of patient cohorts have demonstrated that particular histopathologic and genetic signatures of cytotoxic lymphocyte reactions provide important prognostic information. Here, we discuss the dual roles of immunity in cancer development, focusing on gastrointestinal malignancies, given the depth of recent insights into the mechanisms underlying these tumors.

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INTRODUCTION

Virchow's[1] perceptive observation of the close association between cancer and inflammation in the nineteenth century anticipated the current interest in the role of immunity in tumor pathogenesis. Recent insights into the dynamics of the tumor microenvironment have begun to clarify the mechanisms underlying tumor-promoting inflammation, which bears striking similarities, as Harold Dvorak[2] articulated, to wounds that fail to heal. Approximately 20% of cancer deaths worldwide are currently linked to unresolved infection and/or inflammation, with gastrointestinal malignancies constituting a significant proportion of this disease burden.[1] Among the most frequent associations are colorectal carcinoma and inflammatory bowel disease, gastric carcinoma and *Helicobacter pylori* infection, hepatocellular carcinoma and chronic hepatitis of diverse etiologies, pancreatic carcinoma and chronic pancreatitis, esophageal carcinoma and chronic gastric reflux, anal carcinoma and human papilloma virus infection, and cholangiocarcinoma and sclerosing cholangitis.[3-9]

Notwithstanding these examples of aberrant immunity fostering tumor initiation and evolution, substantial data also support a protective role for immunity in tumor suppression. Paul Ehrlich's[10] original notion of a cancer immunosurveillance system at the turn of the twentieth century has been refined, through elegant studies of cancer development in genetically engineered immune deficient mice, to the contemporary, broader concept of immunoediting. In this scheme, host immunity may eliminate incipient tumors or restrain the growth of established tumors through effectuating a state of equilibrium; disease progression reflects escape from immune control. Several recent clinicopathologic studies provide suggestive evidence that immunoediting might be operative in diverse human malignancies as well.

Here, we highlight progress in elucidating these dual roles of immunity in cancer pathogenesis, with a focus on selected gastrointestinal cancers. Colorectal carcinoma, hepatocellular carcinoma, and gastric carcinoma have been chosen for detailed discussion since progress in understanding these tumors is proceeding at an especially rapid pace. Moreover, the principles revealed with these tumors are likely to be operative in other cancers as well. We first will examine the mechanisms underlying tumor-promoting inflammation, and then turn to the tumor protective pathways, which are tightly linked to patient outcomes. A deeper understanding of host-tumor interactions should advance the crafting of new therapies aimed at more effectively interfering with tumor-promoting inflammation or intensifying immune-mediated tumor destruction. Such strategies might additionally prove complementary to targeted treatments directed at defects intrinsic to cancer cells.

MECHANISMS OF TUMOR-PROMOTING INFLAMMATION

Overview

Unresolved inflammation generates a microenvironment that is favorable for cellular transformation and the propagation of invasive disease.[1,11] Chronic tissue damage triggers a repair response that includes the production of growth and survival factors, tissue remodeling enzymes, angiogenic cytokines, and immune regulatory networks. The release of inflammatory cell-derived reactive oxygen species coupled with stimulated epithelial cell proliferation creates an elevated risk of mutagenesis. Persistently stressed cells may undergo selection for rare variants that manifest increased survival within the inflammatory milieu. The induction of an epithelial-to-mesenchymal transition as part of a program for wound healing may also favor the acquisition of stem cell-like features and invasive capabilities. These properties, together with new blood vessel formation elicited by injury, may foster the evolution of metastasis. Cross-talk between neoplastic cells and immune elements throughout the smoldering inflammation perpetuates the transforming environment, which provides the evolving tumor cells with sufficient opportunity to acquire mutations and epigenetic alterations that are necessary for cell autonomy. Below, we illustrate these complex dynamics within the context of specific gastrointestinal tumors.

Colorectal Cancer

The pathogenesis of inflammatory bowel disease (IBD) is multifactorial and represents a complicated interplay among immune components that predispose to invasive cancer. Patients with IBD, especially those with ulcerative colitis, have a significantly increased risk of colorectal cancer, with an incidence approaching 43% in the 25 to 35 years from the time of diagnosis.[3] Blockade of tumor necrosis factor (TNF) -α with antibodies or soluble receptors is an important component of IBD therapy, and despite its name, TNF-α appears to function as a potent tumor promoter. TNF-α enhances cancer cell survival and augments vascular permeability, facilitating extravasation of tumor cells into the circulation and systemic dissemination.[12] In mouse models, the administration of dextran sulfate sodium (DSS) followed by azoxymethane (AOM) recapitulates important features of human IBD, including the progression to colon cancer.[13,14] This regimen elicits increased intracolonic TNF-α expression, with infiltration of inflammatory cells harboring the TNF-α receptor p55.[15] TNF-α receptor p55–deficient mice treated with DSS and AOM develop less inflammation in the colon and form fewer colonic tumors compared to wild-type animals. Furthermore, the infusion of a TNF-α antagonist to DSS and AOM treated wild-type mice reduces the number of infiltrating inflammatory cells, particularly neutrophils, mast cells, and macrophages, with a concomitant reduction in carcinoma formation. These findings highlight a key role for TNF-α in chemically induced colitis and carcinogenesis.

One of the major signaling events that TNF-α triggers in both tumor and immune cells is the nuclear factor-κB (NF-κB) pathway. NF-κB refers to a family of transcription factors that regulate multiple inflammatory cytokines, adhesion molecules, antiapoptotic proteins, angiogenic factors, and the prostaglandin biosynthetic pathway (through cyclo-oxygenase-2 [COX-2]).[16] NF-κB proteins are normally retained in the cytoplasm through a set of inhibitory proteins, but following receptor-mediated activation of IκB kinases (IKK), the inhibitors are degraded, thereby allowing nuclear import of the transcription factors.[17] Studies of mice deficient in IKK-β have revealed a critical role for this pathway in AOM/DSS-induced colon tumors.[18] Selective deletion of the *IKK-β* gene in intestinal epithelial cells reduces tumor formation, in part because of an increase in enterocyte apoptosis due to the lack of Bcl-2 and Bcl-xL. *IKK-β* deletion in myeloid cells also inhibits tumor progression, which reflects the diminished production of inflammatory mediators, such as interleukin (IL) -6 and epithelial growth factors. These results are consistent with clinical data indicating that nonsteroidal anti-inflammatory drugs, which antagonize the NF-κB target gene *COX-2*, reduce the risk of colorectal carcinoma by 75% to 81% in patients with IBD.[19,20] Furthermore, the Cancer Prevention Study II Nutrition Cohort, which included more than 18,000 patients, documented a 30% decrease in sporadic colon cancer incidence with the use of a daily adult strength aspirin for over 5 years.[21] Together, these investigations reveal a dual requirement for NF-κB signaling in both the target cell and the inflammatory cells during the pathogenesis of colon cancer.

In addition to TNF-α, NF-κB signaling may be activated during colon carcinogenesis through toll-like receptors (TLRs) that are expressed on various myeloid cells, some lymphocytes, and intestinal epithelia.[22] TLRs may be stimulated by conserved biochemical structures expressed by commensal flora. Most TLR signaling proceeds through the adaptor protein MyD88, which is required for the subsequent activation of NF-κB. When mice deficient in MyD88 were introgressed with multiple intestinal neoplasia mice that harbor mutations in the Apc tumor suppressor, fewer polyps were observed compared to mice with intact MyD88 function.[23-26] The major contribution of MyD88 was on polyp growth and progression rather than tumor initiation, reminiscent of the impact of myeloid-specific deletion of *IKK-β* mentioned earlier. Expression profiling analysis revealed that MyD88-dependent signaling contributed to the induction of both tumor-specific modifier genes and genes involved in intestinal tissue repair. These results highlight the close link between wound responses and tumor formation.

A second pathway that functions in concert with NF-κB involves the signal transducer and activator of transcription proteins (STATs). These factors relay signals from extracellular stimuli and act as transcription factors that regulate many genes involved in tumor progression, including cell cycle proteins, antiapoptotic molecules, angiogenic factors, and matrix metalloproteinases.[27-30] There are seven known members of the STAT family, but STAT-3 in particular has been linked to tumor-promoting inflammation. STAT-3 may become activated in tumor cells initially in response to a variety of growth factors, such as IL-6, IL-10, and epidermal growth factor. However, once activated, STAT-3 triggers the production of additional soluble factors that create a feed-forward loop that involves both tumor cells and stromal components. This circuitry creates a procarcinogenic microenvironment that is maintained throughout disease progression.[28-30] Interestingly, an enterotoxigenic strain of *Bacteroides fragilis* that was recently implicated in colon carcinogenesis in both humans and mice is a potent inducer of STAT-3 activation.[31] The critical role of this transcription factor in colon carcinogenesis is also underscored by the reduced incidence of AOM/DSS triggered tumors in STAT-3 deficient mice.[13,14,30]

STAT-3 signaling has a decisive influence on the mixture of cytokines present in the tumor microenvironment, favoring the production of tumor-promoting factors. IL-6 is one of these critical mediators, as tumor growth can be attenuated in murine models through the pharmacologic administration of an IL-6 inhibitor.[30] Since IL-6 serum levels correlate with tumor size in patients with colon cancer,[32-34] these findings have potential clinical relevance. A second important STAT-3 associated cytokine is IL-23, which is expressed at high levels in human colon carcinoma tissues.[35] IL-23 enhances macrophage and granulocyte infiltration that perpetuates inflammation, and cooperates with IL-6 and TGF-β for the differentiation of a newly identified CD4$^+$ T cell subset called Th17 cells. These lymphocytes produce high levels of the cytokines IL-17A and IL-17F that promote angiogenesis, whereas mice lacking these factors show reduced tumor formation.[36,37] IL-23 also limits the development of protective antitumor responses through inhibiting the recruitment of cytotoxic CD8$^+$ T lymphocytes and instead favoring forkhead box protein P3 (FoxP3$^+$) regulatory T cells (Tregs) that further antagonize antitumor cytotoxicity.[38] Through this complex array of soluble factors and cellular subsets, STAT-3 is a major driver of tumor promoting inflammation, and the development of small molecules that inhibit STAT-3 function might afford significant clinical benefits.

In addition to excessive production of inflammatory mediators, IBD can also result from a deficiency in negative immune regulators. Recent genetic analysis uncovered loss of function mutations in the receptor for IL-10 in some families with early onset IBD.[39] These results are in accordance with work in murine models that established a requirement for IL-10 in intestinal immune homeostasis; indeed, mice deficient in this cytokine or receptor develop severe enterocolitis that progresses to colon carcinoma.[40-42] IL-10 has pleiotropic effects on lymphocytes, granulocytes, and macrophages, which together result in a dampening of inflammatory responses.[43,44] Excessive intestinal inflammation and colon cancer similarly occur in mice that are deficient for TGF-β, whereas mutations in the TGF-β receptor are frequently detected in patients.[32,45] Intestinal inflammation may also reflect a deficiency in Tregs, a specialized CD4$^+$ T cell subset expressing the FoxP3 transcription factor, which normally function to restrain innate and adaptive immune reactions. Indeed, the adoptive transfer of Tregs can mediate therapeutic effects in some mouse models, including multiple intestinal neoplasia mice with mutations in the Apc-tumor suppressor gene.[46,47] The reversal of polyposis in this model was associated with a decrease in COX-2 expression, which is consistent with the therapeutic effects of COX-2 inhibitors in humans, as well as a reduction in mastocytosis.[48-50]

Gastric Cancer

Gastric cancer is the second most common cancer worldwide, and chronic inflammation appears to drive the progression from chronic gastritis to gastric atrophy, intestinal metaplasia, dysplasia, and ultimately gastric cancer.[51,52] While infection with *Helicobacter pylori* is very common in human populations, only approximately 1% of exposed individuals develop gastric cancer in response to persistent infection.[4] The subset of patients who progress to gastric cancer appear to have polymorphisms in proinflammatory cytokines, particularly IL-1β, that leads to enhanced levels after bacterial infection,[4] although pathogen specific factors also play important roles.[53] IL-1β has profound effects on inflammation and immunity, in part by inducing MyD88-dependent NF-κB activation, which may engender myeloid-derived suppressor cells that promote tumor angiogenesis and restrain protective cytotoxic lymphocyte reactions.[54,55] In a transgenic mouse model of gastric cancer, the administration of an IL-1 receptor antagonist blocked the progression from chronic gastritis to invasive cancer, in conjunction with the inhibition of myeloid-derived suppressor cell mobilization and recruitment.[56]

Helicobacter-associated gastric tumors show some common pathogenetic mechanisms as the colitis-induced colon tumors. Indeed, bacterial infection activates STAT-3 signaling to promote stomach carcinomas,[57] whereas IL-10 deficient mice develop a more severe form of gastritis.[58-60] In this system, CD4$^+$ T cells and interferon gamma cooperate to trigger severe inflammation.[61]

Hepatocellular Carcinoma

Chronic hepatitis due to infection with hepatitis B and C viruses, alcohol, or toxins is the major risk factor for the development of hepatocellular carcinoma. One informative model for investigating the underlying mechanisms is the *Mdr2*-knockout mouse, which manifests progression from periductular and periportal inflammatory infiltrates to dysplasia, dysplastic nodules, invasive carcinoma, and metastasis.[62] NF-κB activation, as measured by p65 nuclear immunostaining, is observed in this system, and this is blocked with the administration of either an anti-TNF-α antibody or COX-2 inhibitors. As in the colitis model, TNF-α appears to promote tumor formation through NF-κB mediated survival pathways in hepatocytes. However, in contrast to these findings, mice lacking IKK-β selectively in hepatocytes showed a marked increase in susceptibility to diethylnitrosamine-induced liver cancers.[63] Tumor formation in this model reflects increased hepatocyte proliferation in response to damage, with Jun kinase signaling and IL-6 production contributing to cell growth. Treatment of mice with antioxidants attenuated tumor development, in part through inhibiting hepatocyte turnover.[63]

While the specific role of NF-κB in this system remains to be clarified fully, other TNF family members appear to contribute to hepatocellular carcinoma development. Patients with chronic hepatitis manifest elevated expression of lymphotoxin-α and -β and associated receptors.[64,65] In a transgenic mouse model of viral-induced hepatitis, increased levels of lymphotoxin initiated a cascade of chemokine production that culminated in a tumor-promoting inflammatory response. Blockade of this pathway with a lymphotoxin receptor antagonist inhibited the progression to carcinoma. A role for IL-1β in tumor pathogenesis is also implicated through the association of particular polymorphisms and the risk of carcinoma development after hepatitis C infection.[66] Finally, a contribution of adaptive immunity to disease pathogenesis was revealed through studies that showed hepatitis B–specific T cells promoted the evolution of hepatocellular carcinoma in mice transgenic for the viral envelope protein.[67]

Collectively, these investigations highlight a complex interplay of target cell damage, proinflammatory cytokines, NF-κB activation, and immune cells in the development of liver cancer.

PROTECTIVE ANTITUMOR IMMUNE RESPONSES AND IMMUNE ESCAPE

While the tumor-promoting function for immunity is well-established, a growing body of evidence indicates that in some cases of gastrointestinal malignancies, endogenous responses may inhibit tumor growth and perhaps modulate the clinical course of the disease. The most extensive data has been amassed in colorectal carcinomas, where intratumoral T-cell infiltrates are strongly linked with patient outcomes. Indeed, the type, density, and intratumoral location of the lymphocyte infiltrate has been shown to be a more informative biomarker than the TNM or Duke's classification.[68,69] In this context, dense infiltrates composed of cytotoxic memory $CD8^+CD45R0^+$ T cells and an associated interferon gamma–related gene signature are tightly associated with a reduced risk of recurrence after surgery and adjuvant chemotherapy, and increased overall survival. In particular, patients with early-stage cancers but an absence of T-cell infiltrates display poor outcomes, whereas subjects with significant tumor burdens but robust T-cell infiltrates manifest improved outcomes. These findings were recently confirmed in an independent cohort of patients with colon cancer, where the favorable prognostic importance of lymphocytes independent of other well-known clinicopathologic features including microsatellite instability was revealed.[70] Together, these data are consistent with the immunoediting hypothesis that was derived in model systems, and raise the possibility that tumor-specific memory T cells may be induced in some patients and perhaps contribute to disease control.

Because $FoxP3^+$ regulatory T cells may restrain the antitumor activity of cytotoxic T cells, the balance of effector and suppressor cells may also prove to be a decisive factor in patient outcome. Indeed, an analysis of 308 patients with hepatocellular carcinoma showed that a high ratio of cytotoxic to regulatory T cells was associated with increased survival, whereas a low ratio was linked to tumor vascular invasion, the absence of tumor encapsulation, and inferior survival.[71] Moreover, a study of more than 250 histopathologically characterized pancreatic adenocarcinomas revealed that a higher density of Tregs in the primary tumor was associated with advanced tumor stage, high tumor grade, and poor survival.[72]

In addition to eliciting a robust regulatory T-cell response, tumors may exploit other pathways to undermine cytotoxic T-cell reactions and thereby accomplish immune escape. One such mechanism is represented by structural or functional abnormalities in the HLA class I antigen processing machinery (APM).[73,74] APM plays a crucial role in the synthesis and expression of the β2-microglobulin/HLA class I heavy chain/tumor antigen-derived peptide complex. This trimolecular moiety mediates the recognition of tumor cells by cognate cytotoxic T cells. As a result of defects or lack of expression of these complexes, tumor cells may become invisible to infiltrating $CD8^+$ T cells. In addition, the frequency of APM deficiencies is increased in high-stage colorectal carcinomas and in those tumors with *Kras* mutations or microsatellite instability.[75]

Gastrointestinal tumors may also express ligands for the stimulatory natural killer (NK) group 2, member D (NKG2D) receptor, which is expressed on NK cells and on some T cells.[76,77] NKG2D signaling results in perforin dependent cytolysis in NK cells and costimulation of cytotoxic T cells. The NKG2D ligands include members of the MHC class I–related chain and the UL16 binding protein families. NKG2D ligand expression is rare on healthy tissues but can be induced by infection,cellular stress, or malignant cell transformation.

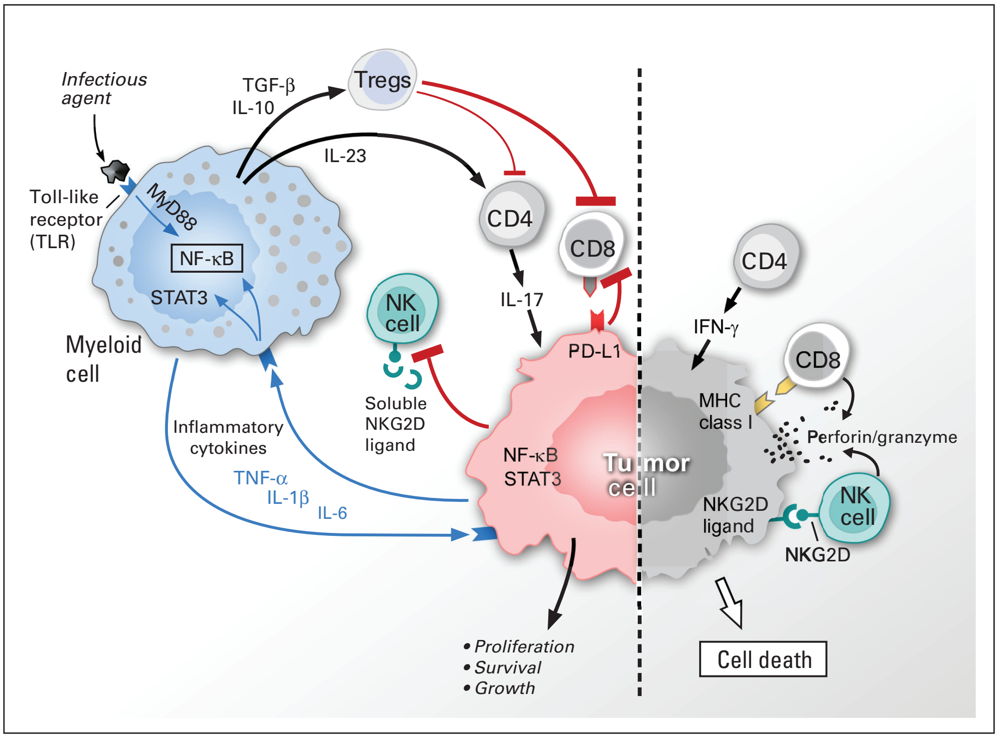

Fig 1. Dynamics of the host-tumor relationship. The overall role of immunity during cancer development reflects the balance of tumor-promoting inflammation and lymphocyte cytotoxicity. Activation of nuclear factor-κB (NF-κB) and signal transducer and activator of transcription protein 3 (STAT3) in tumor cells and myeloid elements by inflammatory cytokines and/or infection enhances cancer cell survival, proliferation, and growth. Interferon gamma (IFN-γ) –secreting $CD4^+$ T cells, perforin/granzyme producing $CD8^+$ T cells, and natural killer (NK) cells mediate tumor destruction. See the text for additional details. TGF, transforming growth factor; Tregs, regulatory T cells; IL, interleukin; TNF, tumor necrosis factor; PD-L1, programmed death ligand 1; NKG, natural killer group.

In human colon cancers, high MHC class I–related chain expression on primary tumors is correlated with improved overall survival.[78] However, tumors may escape immune control in part through the shedding of NKG2D ligands, which induces downregulation of receptor expression and inhibition of NKG2D-dependent cytotoxicity. In patients with gastric cancer, the significant NKG2D downregulation on circulating $CD8^+$ T was correlated with more aggressive and advanced tumors.[79]

Programmed death-1 (PD-1) is a critical negative regulator of T-cell function that is induced on lymphocyte activation.[80] Signaling through PD-1 may be triggered through engagement of the ligands PD-L1 or PD-L2. Interestingly, some tumors upregulate the expression of PD-L1, resulting in dampened $CD8^+$ T cell responses. Studies of patients with pancreatic adenocarcinoma or cholangiocarcinoma have demonstrated that high levels of intratumoral PD-L1 are associated with minimal T-cell infiltrates and poor survival.[81,82] Antibody blockade of PD-1/PD-L1 interactions enhances immune-mediated tumor destruction in experimental models, and initial clinical trials of this approach are underway.

THERAPEUTIC IMPLICATIONS

This review has highlighted the key roles that immunity plays in tumor promotion and tumor protection (Fig 1). One effective strategy to attenuate smoldering inflammation is prevention or eradication of persistent infections. Vaccinations against hepatitis B virus and human papilloma virus have substantively reduced the incidence of hepatocellular carcinoma and squamous cell carcinomas.[83,84] *Helicobacter pylori* can be eradicated with antibiotics, and if this is accomplished before irreversible alterations in the gastric mucosa, the risk of cancer can be decreased.[85] Nonetheless, vaccines against this bacterium and other viral causes of hepatitis are urgently needed.

In certain patient populations, the use of anti-inflammatory agents can reduce the risk of developing cancer. In a randomized clinical trial, the administration of celecoxib diminished not only the cumulative adenoma incidence but also the frequency of advanced adenomas.[48,49] In patients with familial adenomatous polyposis, celecoxib and sulindac decrease the incidence of colorectal and duodenal polyps, which are both precursors for invasive malignancies.[86,87] However, a more complete understanding of the mechanisms underlying tumor-promoting inflammation has identified several compelling novel targets for intervention, including STAT-3 and NF-κB signaling pathways, and associated cytokines such as TNF family members IL-6, IL-1, IL-23, and IL-17.

Complementary strategies might focus on augmenting antitumor cytotoxic T-cell responses and inhibiting $FoxP3^+$ regulatory T cells. In this context, antibody blockade of cytotoxic T lymphocyte associated–antigen 4, a key mediator of Treg suppression and a negative regulator of effector T-cell function, is in advanced stages of clinical testing in melanoma, with encouraging antitumor effects and manageable toxicities.[11,88,89] Interestingly, inflammatory pathology in the gastrointestinal tract is an important adverse effect of this approach, which underscores from a different perspective the dual roles of immunity in cancer.

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